

b.) Remarks

Claims 1 and 42-44 have been amended in order to recite the present invention with the specificity required by statute. In particular, claims 1, 43 and 44 are amended to delete polyoxyethylene alkenylamine as the non ionic surfactant. Claim 42 is amended to correct its antecedent basis only. Accordingly, no new matter has been added.

Claims 1-3, 38, 39 and 41-50 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Takayuki (JP 09-285298), Hama (WO 97/40376) and Miyauchi (U.S. Patent No. 5,736,406) in view of Miki (U.S. Patent No. 6,162,607).

The Examiner's bases of rejection are set forth at pages 3-7 of the Office Action. Therein, Takayuki and Hama are said to teach measuring HDL cholesterol by treating a sample with a nonionic surfactant, cholesterol esterase and cholesterol oxidase in the presence of albumin. These references do not show Applicants' particular choice of a polyoxyethylene alkylamine nonionic surfactant.

As to that, the Examiner acknowledges the effectiveness of Applicants' combination (see page 7) but contends

"Miyauchi et al. clearly teach that one of skill would know to choose any of the many listed detergents, including those disclosed in the instant kits."

This rejection is respectfully traversed.

By way of background, Takayuki teaches measuring HDL-cholesterol by treating a specimen with a cholesterol esterase and cholesterol oxidase in the presence of albumin. The specimen is treated with a sulfated polysaccharide (in particular, dextran sulfate) and nonionic surfactant.

Hama teaches specifically assaying HDL cholesterol by contacting serum or plasma samples with cholesterol esterase, cholesterol oxidase and bile acid, in the presence of albumin, and a nonionic surfactant.

Neither Takayuki nor Hama expressly or inherently teach any method wherein the nonionic surfactant is polyoxyethylene alkylamine as explicitly recited in claim 1, lines 6-7.

According to the Examiner, this deficiency is remedied by Miyauchi and Miki. As relied upon by the Examiner at page 5 of the Office Action, Miyauchi specifically teaches

"the protein solubilizing agent for determining the amount of HDL cholesterol in the sample, cationic, anionic and nonionic surfactants and a bile acid salt are especially preferable among the surfactants such as compounds (VI), (VII) and (VIII) and the bile acid. Examples of the cationic surfactant include oxyethylene dodecylamine, polyoxyethylene dodecylamine and polyoxyethylene octadecylamine. Examples of the anionic surfactant include sodium cocolymethyltaurate, sodium lauroylmethyltaurate, sodium myristoylmethyltaurate, sodium palmitoylmethyltaurate and sodium stealoylmethyltaurate. Examples of the nonionic surfactant include polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether, polyoxyethylene oleyl ether and polyoxyethylene behenyl ether. Examples of the bile acid salt include sodium cholate, sodium deoxycholate, sodium chenodeoxycholate, sodium ursodeoxycholate, sodium lithocholate, sodium isochenodeoxycholate, sodium 7-oxolithocholate, sodium 12-oxolithocholate, sodium 12-oxochenodeoxycholate and sodium 7-oxodeoxycholate."

Miki is simply relied upon as teaching use of nonionic polyoxyethylene oleyl ether surfactants for measuring HDL, particularly those having HLB values of 12 to 17, in combination with cholic or deoxycholic acid.

According to the Examiner, therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods disclosed by Takayuki based upon Hama, Miyauchi and Miki to attain the present invention.

As noted, Applicants above amended claim 1 to recite polyoxyethylene alkylamine as their particular nonionic surfactant. As shown in the specification as filed, the claimed method for quantitatively determining HDL cholesterol unexpectedly permits quantitatively determining HDL cholesterol even in sera samples originated from patients suffering from M proteinemia. Applicants attribute this unexpected result to the claimed combination of albumin, dextran sulfate and polyoxyethylene alkylamine, as shown in Example 59 and Comparative Example 31 and explained in detail below for the Examiner's convenience.

Example 59 (specification page 100) and Comparative Example 31 (specification page 101) show quantitatively determining HDL cholesterol in sera samples originated from patients suffering from M proteinemia respectively using the kits of Example 1 (specification page 56) and Comparable Example 5 (specification page 62). The kit of Example 1 comprises the nonionic surfactant "Nymeen L207" (which is polyoxyethylene alkylamine) and dextran sulfate as a polyanion. The kit of Comparable Example 5 is the same as the kit of Example 1, but without dextran sulfate. Example 59 corresponds to the method of amended claim 1.

As is seen in Table 7 at specification page 102, HDL cholesterol in sera samples originated from patients suffering from M proteinemia can be determined correctly using the kit of Example 1, while HDL cholesterol in sera samples originated from such patients cannot be determined correctly using the kit of Comparable Example 5. This very desirable result is completely unexpected in view of the prior art.

Regardless, in the Office Action, the Examiner states that Miyauchi clearly teaches that one of skill would know to choose any of the many listed detergents, including those disclosed in the instant claims, and also that the named cationic, anionic and nonionic detergents listed are only examples of the surfactants available to one of skill in this art.

However, Miyauchi¹ neither teaches nor suggests that Applicants' specific polyoxyethylene alkylamine nonionic surfactant, taken together with albumin and dextran sulfate, enables the correct determination of HDL cholesterol in sera samples as evidenced above.

Solely in order to reduce the issues, then, and to complete the record, Applicants have prepared and enclose a Declaration of Yuki Katayama, one of the inventors of the present invention, conclusively showing that the claimed method using albumin and a combination of dextran sulfate and polyoxyethylene alkylamine permits correctly determining HDL cholesterol even in sera samples originated from patients suffering from M proteinemia, while methods using albumin and a combination of dextran sulfate and nonionic surfactants other than polyoxyethylene alkylamine (such as those disclosed in Miyauchi, e.g., polyoxyethylene lauryl ether, polyoxyethylene cetyl ether,

¹ Nor Takayuki, Hama or Miki.

polyoxyethylene stearyl ether, polyoxyethylene oleyl ether, polyoxyethylene monolaurate and polyoxyethylene monostearate) do not permit correctly measuring HDL cholesterol in such sera samples.

This is direct, uncontroverted, secondary evidence of the nonobviousness of the present invention.

Subsequent to *KSR*, the Court of Appeals for the Federal Circuit, District Courts and the Board of Patent Appeals and Interferences have all confirmed this very point: that post-*KSR*, a showing of unexpected results may continue be used to rebut a showing of obviousness by the Examiner. For example, in *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293, 13401 (Fed. Cir. 2007), citing *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990), the court held that once a *prima facie* case of obviousness is established, the applicant may rebut it by showing the claimed invention has unexpected properties. Similarly, in *Ricoh Company, Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1331-1332 (Fed. Cir. 2008), the court held that the presumption of obviousness could be rebutted if the claimed range of the invention produced unexpected results. Likewise, in *McNeil-PPC, Inc. v. Perrigo Company*, 516 F.Supp.2d 238 (S.D.N.Y. 2007), after explaining the legal standard set forth in *KSR*, the court explicitly affirmed that a showing of unexpected results may sufficiently rebut a *prima facie* case of obviousness. *Id.* at 255, citing *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006), and *In re De Blauwe*, 736 F.2d 699, 706 n.8 (Fed. Cir. 1984).

Therefore, Applicants submit that the presently claimed invention is not rendered obvious by Takayuki, Hama, Miyauchi and Miki, independently or in combination.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 1-3, 38, 39, 41-46, 48 and 49 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

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